37. (Currently amended) The method according to any one of Claims 33-35 ~~36~~, wherein said CD8 α-chain consists essentially of a CD8 α-chain extracellular domain and a transmembrane domain.

38. (Canceled)

39. (Currently amended) The method according to Claim 37 ~~or 38~~, wherein said transmembrane domain is a CD8 α-chain transmembrane domain.

REMARKS

Claims 1, 5, 6, 14-15, 17-26, 33-37 and 39 are pending. Claims 18-26 are withdrawn. Claims 2-4, 7-13, 16, 27-32 and 38 have been canceled. Claims 1, 5, 6, and 33-35 have been amended as described herein. Claims 15, 17, 37 and 39 have been amended to correct improper multiple dependencies. These amendments add no new matter. Applicants respectfully request the entry of these amendments.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Election/Restriction

The Office Action of November 30, 2006, characterized claims 18-24 as nonelected with traverse. Action at page 2. Applicants respectfully point out that the 12/17/05 election made in response to the Office's 11/21/2005 restriction requirement was made without traverse.

Claim Objections

Applicants thank the Examiner for pointing out improper multiple dependences of claims 15-17 and 37-39. Applicants have amended claims 15, 17, 37 and 39; and have canceled claims 16 and 38. The amended claims are free of improper multiple dependencies, rendering these objections moot.

Declaration under 37 C.F.R. § 1.132

Applicants point out that a declaration executed May 25, 2006, accompanies this response. This is a second declaration by the Applicants' Chief Scientific Officer, Dr. Uwe D. Staerz and shall be referred to herein as Dr. Staerz's 2nd Declaration.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 5, 6 and 33-36 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner generally asserts that "[t]he specification does not reasonably provide enablement for inhibiting any immune response (Claim 1 and dependent claims), any portion of the CD8-alpha chain, or any CTL response." Action at page 3.

Applicants respectfully traverse. Applicants submit that the specification does enable one of skill in the art to practice the invention commensurate in scope with the currently-pending claims without undue experimentation. Applicants address each of the Office's concerns regarding the breath of the claims as outlined below. *In re Wands*, 858 F.2d 731, 737, 8 UDPQ2d 1400, 1404 (Fed. Cir. 1988); MPEP 2164.01(a).

Applicants' data establishes that both CD8+ CTLs and CD4+ T cells are inhibited by the subject methods, including fully-activated T Cells

In rejecting the claims for enablement based on the nature of the immune response affected by the subject methods, the Examiner suggests that "it is clear that only adaptive CTL immunity is affected, and not other forms of immune reaction." [Office Action at p. 4]. The Examiner further asserts based on paragraph [0173] of the specification that antigen specific CTLs cannot be inhibited. In response, Applicants have adopted one of the Examiner's suggestions and amended the claims herein to clarify that "adaptive" T cell responses are inhibited by the subject methods. Significantly, however, Applicants also traverse in part the Examiner's rejection and provide further detail on the particular experiment noted by the Examiner as well as other experiments described in the specification, which taken together support rather than contradict Applicants' contention that both CD8+ and CD4+ T cell responses can be inhibited by the subject methods, including activated antigen-specific T cells.

As explained in Dr. Staerz's 2nd Declaration submitted herewith, the data and results referenced by the Examiner in Figure 5A represent an initial experiment performed to determine whether cell surface expression of the CD8 alpha chain could interfere with fully-activated T cells. Notably, however, the experimental protocol employed alloreactive CTLs present in a

mixed lymphocyte culture sensitized in bulk to alloantigen, and this mixed culture also included NK cells and lymphokine-activated killer (LAK) cells. [Dr. Staerz 2nd Declaration at paragraph 8. Thus, the actual effector cell population employed in this experiment was undefined in that other effector cell types such as activated NK cells were also present which likely accounted for the efficient lysis seen in the results. [*Id*]. In light of this anomalous result Applicants therefore designed a second experiment with a better-defined cell population limited to T cells and excluding other effector cell populations. The results of this experiment are presented in Figure 5B and clearly establish that antigen-specific T cells are effectively inhibited by CD8 alpha chain expression. Moreover, Applicants further demonstrated that the subject methods could inhibit CD4+ T cell responses in addition to CD8+ CTLs, a surprising finding that was contrary to the then-accepted belief in the art. [Dr. Staerz 2nd Dec at paragraph 9.

Accordingly, the data provided by Applicants in their specification fully supports and enables the scope of the presently-claimed methods, which have been clarified herein to encompass the inhibition of adaptive T cell responses to alloantigens expressed on a target cell. Applicants therefore respectfully request reconsideration and withdrawal of the Examiner's enablement rejection on this basis.

A "functional portion" is clearly defined in the specification

The Examiner also asserts that the claims lack enablement for "any" portion of the CD8 alpha chain, arguing in particular that "the functional portion, which encompasses intracellular domains only, or transmembrane domains only, is not enabled for its full scope." Applicants respectfully traverse, since the claim phrase "all or a functional portion of a CD8 alpha chain" is clearly and explicitly defined in the specification to include, at a minimum, the Ig-like domain in the extracellular region of the CD8 alpha chain responsible for HLA-binding activity. [*See* Specification at paragraph [0070]. As the Examiner is well aware, Applicants can be their own lexicographer in the specification and in this instance have expressly defined their claim phrase "all or a functional portion thereof" such that the functional portion cannot be solely the intracellular or transmembrane domains as the Examiner suggests. To the contrary, the phrase is defined appropriately to include at least the HLA-binding portion of the extracellular domain and as such the resulting claim scope is fully enabled.

Applicants respectfully submit that this definition obviates the Examiner's concerns regarding the nature of the CD8 alpha chain expressed on the target cell, and thus request reconsideration and withdrawal of the 112 rejection based on the recitation of "all or a functional portion of a CD8 α-chain" in claims 1, 5, 6 and 33-35, and claims depending therefrom.

Suryaprakash et al. is not determinative of the claimed in vivo method

Citing Suryaprakash et al. (1991) Science, 252: 1424-27, pp. 1424-25, the Examiner also asserts that intravascular injection of a vector at a site proximate to target cells "at any time point (Claim 35) or prior to or during transplantation" is not enabled for any point after 2 days-post transplant. Action at page 4. As detailed in Dr. Staerz's 2nd Declaration, paragraph 10, however, the Suryaprakash article involved *in vitro* rather than *in vivo* studies, and Suryaprakash's *in vitro* findings are not automatically determinative of an *in vivo* approach.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the 112 rejection directed towards claim 35.

Enough cells are transformed in vivo

The Examiner also alleges that claims 33-36 lack enablement with respect to additional *in vivo* aspects. Action at pages 4-5. Specifically, the Examiner contends that it is not reasonably predictable that enough cells would be transformed due to circulatory clearance, and cites Applicants' Example 3 as showing that particular tissues are refractory to transformation. *Id.* Applicants consider that the Examiner is referring to the statement with respect to the skin transplants of Example 3 that "tolerance was not induced and the skins eventually succumbed to rejection, apparently due to the later-determined fact that the majority of skin cells are refractory to infection with adenoviral vectors." Specification, paragraph 0217.

Applicants respectfully refer the Office to Dr. Staerz's 2nd Declaration, paragraphs 11-14. As explained in more detail therein, the skin transplant data actually demonstrates the efficacy obtainable using the subject methods despite low transduction frequencies. While *in vivo* transduction in skin cells was less than 0.5%, rejection was unmistakably delayed and reduced due to the veto effect obtained. Further, additional techniques known to the skilled artisan provide even better transduction, e.g., by overcoming clearance using "kidney loading" or

recycling after kidney pass-through. These art-known techniques are discussed in greater detail in Dr. Staerz's 2nd Declaration, paragraph 13.

Accordingly, Applicants respectfully submit that the currently-pending claims are adequately supported by Applicants' experimental data and in full compliance with the requirements of 35 U.S.C. §112, first paragraph. Applicants request reconsideration and withdrawal of the enablement rejections directed at claims 1, 5, 6 and 33-36.

Further, as the Examiner acknowledges that claims 33-36 are free of the art of record (Action at pages 7- 8), Applicants note that these claims are in condition for allowance upon the withdrawal of the 112 rejections.

Rejections under 35 U.S.C. §102(b)

The Examiner has reiterated the previous anticipation rejection of Claims 1, 5, 6 and 14 under 35 U.S.C. §102(b) by U.S. Patent Application No. 2002/0127205, Edge et al. (hereinafter "Edge"), asserting that the claims fail to exclude the possibility of inclusion of the CD8 β chain in the expression vector. Applicants respectfully traverse, since the claims as presently amended require the expression vector to encode a CD8 polypeptide limited to all or a functional portion of the CD8 α chain. As such, the CD8 polypeptide encoded by Applicants' vector could not also further include the CD8 β chain taught by Edge et al., thus resolving the anticipation rejection.

Moreover, as detailed by Dr. Staerz in his 2nd Declaration at paragraphs 4-7, the conventional view in the art as of the priority date of the instant case was that soluble CD8 was necessary to effectuate veto. The cursory disclosure provided in Edge regarding CD8 veto fails to contravene this general view, and in fact the genomic sequence for CD8 α used by Edge in preparing its CD8 construct would produce both soluble and cell-surface expressed forms of the α chain. [*See* Dr. Staerz's 2nd Declaration, paragraph 7]. Applicants have further amended the claims herein to explicitly recite the inclusion of a transmembrane domain for cell surface expression of the CD8 α chain, a feature which clearly distinguishes Applicants' approach from the conventional soluble CD8 approach espoused in the prior art, including the above as well as WO 02/102852 referenced in Applicants' specification. Notably, WO 02/102852 further discloses that their soluble CD8 approach is limited in effect to MHC Class I-restricted (e.g.

CD8+) T cells, and hence this reference also evidences the surprising results obtained with Applicants' cell surface expression approach, which can also effectively inhibit MHC Class II-restricted (e.g. CD4+) T cells.

When properly considered in its entirety, it is clear that the Edge disclosure cannot be relied upon as an enabled prior art teaching of the cell surface expression of CD8 α chain alone as presently claimed. Applicants respectfully direct the Examiner's attention to M.P.E.P. §2121.01, which states:

> In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure' ..." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 168). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. Elan Pharm. Inc., v. Mayo Found. For Med. Educ.& Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

In the present case, the Edge disclosure fails to name or describe the subject matter as presently claimed and, accordingly, cannot anticipate Applicants' invention. For at least the foregoing reasons, Applicants maintain that their invention as presently claimed is both novel and non-obvious in view of the teachings in the art, including those cited by the Examiner, and as such withdrawal of the anticipation rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and respectfully request notice of the same at the Examiner's convenience. Should there by any remaining issues the Examiner is welcome to contact Applicants' representatives by telephone at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: 5/25/07

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